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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control

Final Recommendations for Protecting the Health and Safety Against Potential Adverse Effects of Long-Term Exposure to Low Doses of Agents: GA, GB, VX, Mustard Agent (H, HD, T), and Lewisite (L)

AGENCY: Centers for Disease Control (CDC), Public Health Service, HHS.
ACTION: Notice of Final Recommendations for Protecting Human Health and Safety Against Potential Adverse Effects of Long-term Exposure to low doses of agents GA, GB, VX, Mustard Agent (H, HD, T). and Lewisite (L).

SUMMARY: Agents GA, GB, VX, Mustard Agent (H, HD, T), and Lewisite (L) are now stored by the Department of Defense (DOD). Public Law 99-145 (50 U.S.C. 1521) mandates that all unitary (self-contained) lethal chemical munitions be destroyed by 1994. Public Law 91-121 and Public Law 91-441 (50 U.S.C. 1512] mandate that the Department of Health and Human Services review DOD plans for disposing of these munitions and make recommendations to protect human health. Public comment was requested on these recommendations; this notice summarizes comments received, responds to those comments and states the final recommendations.

EFFECTIVE DATE: March 15, 1988.
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SUPPLEMENTARY INFORMATION: On December 22,1987, the Department of Health and Human Services (HHS) Centers for Disease Control (CDC) published "Recommendations for Protecting the Health and Safety Against Potential Adverse Effects of Long-Term Exposure to Low Doses of Agents: GA, GB, VX, Mustard (H, HD, T). and Lewisite (L)" in the Federal Register (52 FR 48458), seeking public comment. We received comments from eight respondents.

One respondent indicated that the recommendations had been sent to several agencies within their organization for review and that they had approved the statement as published. Two other respondents objected to the use of "weak" to characterize the carcinogenicity of mustard agent. Both pointed out that the term is not used by the International Agency for Research on Cancer,' one noted further that the National Toxicology Program has not accepted "weak" as a standardized descriptive term. The specific terms "strong" and "weak," as applied to carcinogens, were once used in extrapolating animal data to human prediction. The way in which that was done is not now generally accepted. We agree: the word "weak" has been deleted.

One respondent objected to the statement " * * Some evidence suggests that Lewisite might be a carcinogen " ***." and referred to a recent comprehensive review of the published literature on Lewisite as well as unpublished reports available in the library of the U.S. Army Chemical Research, Development, and Engineering Center at Edgewood Arsenal. The respondents concluded, from their review of the literature, that Lewisite was not carcinogenic. Th documents do mention the same evidence for carcinogenicity which was considered by the group. We agree that the evidence available to us does not seem to be of the quality required to label a chemical as a "suspected carcinogen" but will stand by the original phrasing, *** S*ome* evidence suggests that Lewisite *might* also be a carcinogen ***." (emphasis added)
We were advised that the NIOSH recommended standard for occupational exposure to arsenic does not distinguish between organic and inorganic arsenic and recommends a standard of 0.002 mg (As)/m^3. The suggested control limit for Lewisite is equivalent to 0.001 mg/m^3, measured as arsenic, and is thus lower than both the OSHA Permissible Exposure Level and NIOSH's more protective recommendation. The same respondent objected to the comparison of cancer risk to risk of death by injury in industries considered nominally safe on the grounds that such a comparison supports the belief that injury rates are acceptable or irreducible. The objection is valid and the comparison has been removed.

Another respondent suggested that the recommendations would be strengthened by references. An extensive bibliography is available on request. The respondent also recommended use of a pressure-demand respirator when entering munition storage igloos. This is in keeping with joint NIOSH-OSHA respiratory selection policy guidelines. Entry into igloos is governed by storage regulations and is not included in the Chemical Stockpile Disposal Program. HHS has no authority in matters concerning storage of chemical weapons. We therefore cannot include this recommendation under Pub. L.91-121, 91-441, or 99-145. We will forward the suggestion to the Army Surgeon General's Office for their consideration.

An unpublished paper on the toxicology of VX was forwarded to us by an interested party. The paper suggested that there was a high probability of serious non-lethal effects with exposure to VX. The doses required to achieve these effects were not specified. Most of the paper was conjecture, based on analogy with other organophosphates. Information available in the open literature describing actual studies 6n VX was not used. These and other weaknesses in the paper rendered it not helpful for our deliberations; we do not concur with the conclusions of that paper.

One respondent reminded us that a portion of the stockpile is held in the Federal Republic of Germany. This was noted. A minor typographical error, "skin" misspelled "kin," was noted by several respondents. In addition to this correction, changes have been made in the text to note the NIOSH recommendation, to convey the sense of the epidemiologic evidence on carcinogenic potency without use of the term "weak," and to delete reference to deaths by injury in industries considered nominally safe. The final text of the recommendations follows.

Recommendations: Section 1412 of Pub. L. 99-145 (50 U.S.C. 1521) mandates that the present stockpile of lethal chemical agents be destroyed by September 30, 1994. Public Law 91-121 and Pub. L. 91-441 (50 U.S.C. 1512 mandate that the Department of Health and Human Services (HHS) review Department of Defense (DOD) plans for transporting and/or disposing of lethal chemical agents and make recommendations for protecting human health and safety. HHS has delegated this authority to the Centers for Disease Control (CDC). In the absence of Federal regulatory standards, DOD has developed safety and health standards for handling these agents. Therefore, CDC reviewed the data and is making recommendations for protecting human health and safety during the transportation and/or disposal of these lethal agents.

The national stockpile of lethal chemical agents includes six chemicals..

GA	(Tabun or ethyl N.N-dimethyl phosphoroamidocyanidate. GAS 77-81-6)
GB	(Sarin or isopropyl methylphosphonofluoridate, CAS 107-44-8)
VX	(O-ethyl-S-(2-diisopropylaminoethyl)-methyl phosphonothiolate, CAS 50782-69-9)
H HD	(Sulfur mustard or di-2-chloroethyl sulfide, CAS 505-60-2)
T	(Bis(2-chloroethylthioethyl) ether, CAS 63918-89-8)
L	(Lewisite or dichloro 2-chlorovinylarsine, CAS 541-25-3)

The DOD stores these agents in bulk containers and/or munitions at eight locations within the continental United States. The remainder of the stockpile is stored outside the continental United States on Johnston Atoll in the Pacific Ocean (Southwest of the Hawaiian Islands) and in the Federal Republic of Germany.

Previously, HHS has made recommendations for protecting human health from the adverse effects of acute exposure to agents GB, VX and mustard agent. Citizens near depots where chemical weapons are stored have expressed concerns about the potential for delayed effects of acute exposure and about the potential health effects of long-term exposure to low doses of agents. (Here “low dose" means an airborne concentration of agent below the control limits.) To resolve these questions, CDC gathered data on these

agents and held an open meeting to discuss the potential delayed effects of acute exposure and of adverse effects of long-term exposure to low doses of these agents. The meeting, announced in the Federal Register dated August 20. 1987 (52 FR 31449), was held September 29-30, 1987, in Atlanta, Georgia The CDC invited consultants and the public. Comments from individuals rather than group comments or consensus were solicited.

Like widely used insecticides, the nerve agents GA, GB, and VX are organic compounds containing phosphorus (organophosphorus compounds). They affect nerves, muscles, and glands by inhibiting acetyl cholinesterase, an enzyme these tissues must have to function properly. Sulfur mustard (H, HD, hereafter referred to simply as "mustard agent") and Lewisite (L) are vesicants- that is, they cause chemical burns or blisters of the skin and mucous membranes, such as the conjunctiva of the eyes and the mucosa of airways. Lewisite is an organic compound containing arsenic. A sixth agent, HT, is a mixture of mustard agent, agent T [bis(2-chloroethylthioethyl) ether),and impurities. Very little is known about the long-term toxicity of agent T. Agent T has much lower volatility than the H with which it is mixed. It is not expected to constitute an airborne hazard unless mustard agent is also present at concentrations much higher than permitted. Almost all (99.97%) of the vapor released by HT is mustard agent. HT control limits will therefore be identical with those for HD, with concentrations measured as HD.

During the public meeting on the potential effects of exposure to these agents, concerns that were raised included: organophosphate-induced delayed neuropathy; electroencephalographic (EEG) or other functional changes following exposure to organophosphates; the carcinogenicity, mutagenicity, and/or teratogenicity of organophosphates; the cumulative effects of organophosphates, decreasing resistance to organophosphorus pesticides; the carcinogenicity, mutagenicity, and teratogenicity of mustard agent and Lewisite; delayed keratitis (injury to the cornea of the eye) following exposure to mustard agent; the response time, sensitivity, and specificity of monitors; the amount of agent in the various parts of the storage and demilitarization facilities; the response times and efficacy of abatement procedures in the event of an upset in plant operations or a release from storage, transportation, or incineration; use of historical monitoring in process control; and interactions of agents with other chemicals in the environment

Published and unpublished reports of all potential adverse effects including carcinogenicity, mutagenicity, and teratogenicity for all agents were considered. Information on human carcinogenicity following wartime exposure to vesicants supplemented experimental data for mustard agent and Lewisite. Since the acute toxicity of GA and Lewisite had not been reviewed before, it was considered along with the potential long-term health effects. Reports relating delayed keratitis to mustard agent exposure were evaluated. The reports on delayed neuropathy and on EEG changes associated with poisoning by GB were available. In addition, individuals contributed critical information from their own experience and knowledge.

The ability of organophosphates to cause delayed neuropathy has been tested in domestic chickens, a sensitive indicator species. The chickens are given doses from 20 to more than 100 times the mean lethal dose and, for the chickens to demonstrate this effect, they must be protected from death by pretreatment with atropine or with atropine and an oxime. GB caused neuropathy in chickens only at doses several times greater than the mean lethal dose. Under similar conditions, VX did not induce delayed

neuropathy. Neuropathy is considered an unlikely outcome from either acute intoxication with any of the nerve agents or from long-term exposure to them.

None of the nerve agents are mutagenic. Results of recently completed studies on GB and initial reports of studies on VX indicate no teratogenic effect. The EEG changes reported after intoxication with GB were considered to be of questionable significance-given the difficulty of
demonstrating such changes and the absence of clinically significant effects even when EEG changes are present.

HHS had not previously reviewed standards for GA. The available information indicates that about twice as much GA as GB is needed to produce acute toxicity. Data for adverse reproductive effects are less complete for GA than for GB. The limited amount of GA present in the stockpile (4 tons) and the remoteness of the area where it will be destroyed (Tooele, Utah) provide further assurances that human health will be protected at the same control concentrations previously set for GB.

Questions related to the nerve agents proved relatively easy to resolve. The information bases are fairly complete, and there appears to be little risk either of adverse health effects from long-term exposure to low doses or of delayed health effects from acute exposure. On the basis of the evidence reviewed, HHS concludes that human health will be adequately protected from exposure to GA. GB, and VX vapor at the concentrations shown in Table 1. Even long-term exposure to these concentrations would not create any adverse health effects. At these concentrations, no detectable reduction in resistance to organophosphorus pesticides would occur,

TABLE 1. -CONTROL LIMITS (mg/m^3) FOR CHEMlCAL AGENTS [1]

Agent	General population	Workers
GA, GB	0.000003 (3×10^{-6})	0.0001 (1×10^{-4}).
VX	0.000003 (3×10^{-6})	0.00001 (1×10^{-5}).
H, HD, HT[2]	0.0001 (1×10^{-4})	0.003 (3×10^{-3}).
L Averaging Time.	0.003 (3×10^{-3}) 72 hours	0.003 (3×10^{-3}) 8 hours.

[1] Protection against exposure to agents in aerosol and liquid form must be sufficient to prevent direct contact with the skin and eyes.

[2] Data supporting the ability to monitor for mustard agent at 0.0001 mg/m^3 at all sites should be developed. HT is measured as HD.

The control limits contained in Table 1 are substantially below concentrations at which adverse affects have been observed for mustard agent and Lewisite. Delayed keratitis and chronic bronchitis are effects that follow acute symptomatic intoxication with

mustard agent and would therefore not be expected at the limits proposed. Mustard agent is not a teratogen -but it is a mutagen. Because HHS accepts that mustard agent is a human carcinogen and because some evidence suggests that Lewisite might also be a carcinogen, lower levels of exposure are of potential concern. Although the data suggest that mustard agent is less potent than such other known human carcinogens as tobacco, radon, and chromates, the data do not permit an estimate of the carcinogenic potency or the exact degree of the carcinogenic risk with confidence. Quantitative risk assessments prepared by the Oak Ridge National Laboratories and by a community study group at Edgewood, Maryland were considered. On the basis of a review of the methodology, we conclude that the many uncertainties in the method employed preclude its being used to define precisely the acceptable exposure limits to mustard agent. We conclude that the proposed work-place limits appear to provide adequate protection for workers during the limited time of potential exposure prior to completion of the. Chemical Stockpile Demilitarization Program. Control of the stack emissions and the work-place air in accordance with the limits for mustard agent given in Tables 1 and 2 will amply protect a general population 1000 meters or more from a demilitarization site or transportation route.

Exposure to or contact with mustard agent by any route-respiratory, skin, or oral-should be limited to the extent practicable. This can be done by using appropriate engineering controls, personal protective equipment, and work practices. Concentrations in the work-place environment and surrounding air should be measured and verified by instruments that can reliably detect concentrations at or below the control limits. Rail cars or other transport vehicles should be treated as work places for this purpose. At this time, the most sensitive monitors can reliably measure 0.003 mg/m^3 of mustard agent and Lewisite in the work place air. The cycle time for mustard agent is 8 minutes-that is, the test is automatically repeated every 8 minutes. The cycle time for Lewisite is 12 hours. This level of exposure would be adequate protection for public health. The Army has reported the capability to monitor for mustard agent at concentrations as low as 0.0001 mg/m^3 using a 12-hour sample time. This capability has been proven under usual ambient conditions at only one site. If it will not delay disposal, it is recommended that such capacity be demonstrated at and used for all sites where mustard agent will be transported or destroyed. The capacity to conduct such monitoring at all sites with mustard agent would represent a redundant safety factor.

Toxicological information specific to Lewisite is sparse. More is known about arsenic-containing compounds in general, but caution must be used in extrapolation. The recommended control concentration limit, 0.003 mg/m^3, (measured as Lewisite) in air is equivalent to 0.001 mg/m^3 measured as arsenic and should be adequate to protect public health. The Occupational Safety and Health Administration has promulgated a standard of 0.5 mg/m^3 (measured as arsenic) for organic arsenic concentrations in work-place air. The National Institute for Occupational Safety and Health (NIOSH) has recommended a standard of 0.002 mg/m^3 for all forms of arsenic. The proposed Lewisite control limits are lower than the existing OSHA occupational standard for organic arsenic by a factor of approximately 500 and are lower than the NIOSH recommended standard by a factor of 2.

The Army should seek, through engineering design and operational controls, to minimize exposure to Lewisite. The facts that Lewisite will be destroyed only at Tooele, Utah, a facility remote from population centers, and that the maximum burning time for destruction of the existing stockpile of Lewisite is estimated to be less than 30 days provide additional assurance that human health will not be endangered.

Certain monitoring criteria are essential because any recommended exposure limit is only as good as the capability to measure and verify the exposure concentrations as they may occur. Specifically, the Army has agreed to provide data to CDC that document accurate and reproducible monitoring for agents at the recommended exposure limits and at each transportation or demilitarization facility monitored.
In summary, the control limits specified in Table I for all agents listed are considered protective of human health. The relatively short duration of the disposal program provides an additional margin of safety.

Control limits for stack emissions are primarily an engineering matter. These limits should (a) be attainable by a well-designed, well-constructed, and well-operated incineration facility; (b) give an early indication of upset conditions; and (c) be accurately measurable in a timely manner.

Limits based on these criteria will restrict emissions to concentrations well below those that would endanger health; they will usually prove more restrictive than a limit set on health bases alone. CDC has found that the allowable stack concentrations proposed by the Department of the Army. (Table 2) meet the criteria above and are more restrictive than limits set on health bases alone; therefore. CDC recommends no changes in the concentrations. The concentrations must be evaluated by air dispersion modeling of worst-case-credible events and conditions specific to each site to ensure that the control limits for the general population and work place (Table 1) would not be exceeded as a consequence of releases at or below the allowable stack concentrations.

TA6LE 2.-ALLOWABLE STACK CONCENTRATIONS (MG/M^3) FOR CHEMICAL AGENTS-

Agent	Maximum allowable stack concentration
GA, GB……..	0.0003 (3×10^{-4})
VX……..	0.0003 (3×10^{-4})
H,HD,HT[1]	0.03 (3×10^{-2})
L	0.03 (3×10^{-2})

[1] HT is measured as HD
Dated: March 8, 1988.
Robert L. Foster,
Acting Director,Office of Program Support Centers for Disease Control.
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